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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,922	04/12/2001	Frederic Geissmann	1383-0260001	8471

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/832,922	GEISSMANN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 02 November 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *02 November 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*.

Claim(s) objected to: *None*.

Claim(s) rejected: *1,2,4,5,10 and 16*.

Claim(s) withdrawn from consideration: *None*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 3. Applicant's reply has overcome the following rejection(s): The rejection of claim 1 and 10 under 35 U.S.C. 102(b) as being anticipated by Trinchieri et al (Blood 69(4): 1218-24, April 1987; PTO 892) is hereby withdrawn in view of the reference HL60 cells are not "antigen-presenting cells" as required by the claimed method.

Continuation of 5. does NOT place the application in condition for allowance because:

The enablement rejection of Claims 1-2, 4-5, 10 and 16 stand rejected under 35 U.S.C. 112, first paragraph for the same reasons of record.
Applicant's arguments filed 11/2/04 have been fully considered but are not found persuasive. Applicants' position is that the examiner's use of the phrase "for treating any disease" is a mischaracterization of the presently claimed invention. The specifciation states that the methods of the presently claimed invention may be used to treat ". . . a physical disorder that may be delayed, prevented, cured or otherwise treated by differentially modulating immune system function . . ." (see, e.g., Specification at page 22). Applicants are not claiming the treatment of any disease, but instead of physical disorders with defined characteristics. Indeed, the use of such methods to treat such diseases is specifically disclosed in the present specification, e.g., at pages 58-72.

In response to applicant's argument that the claimed invention may be used to treat "...a physical disorder that may be delayed, prevented, cured or otherwise treatd by differentially modulating immune function, the specification does not teach which particular physical disorders and what characteristics are associated with said physical disorder "may be treated" by the claimed method. Further, the term "modulating" encompasses stimulating and inhibiting in which the action is mutually exclusive. There is insufficient guidance as to contacting antigen-presenting cell in an animal with which retinoid such as pan-RXR agonist, RAR antagonist and which cytokine and combination thereof would affect the physiology of which antigen presenting cell and thereby inhibiting the immune system to treat which physical disorder. There is insufficient guidance as to contacting antigen-presenting cell in an animal with which retinoid such as pan-RXR agonist, RAR antagonist and which cytokine and combination thereof would affect the physiology of which antigen presenting cell and thereby stimulate the immune system to treat which physical disorder.

In contrast to applicant's assertion that pages 58-72 disclsoes method to treat diseases or physical disorders with defined characteristics, pages 58-72 discloses various screening methods, not treating diseases as argued.

In response to applicant's argument on page 8 that the specification teaches how to make a number of RXR and RAR agonist and antagonist and "Compounds II, V and VIII" are specific compounds having specific structures, although the specification teaches how to make said compound, the specification does not teach how to use in terms of the "effective amount" of retinoid and cytokine combination to affect the physiology of which antigen presenting cell in animal as a method to inhibit the immune system. Likewise, there is insufficient guidance as to the "effective amount" of which retinoid and which cytokine combination to affect the physiology of which antigen presenting cells in animal as a method to stimulate the immune system of an animal.

In response to applicant's argument on page 9-11 that the the present specification discloses a nubmer ways in which cytokines both natural and synthetic can be procured (specification at page 72-73), the specification merely lists a number of cytokines. The specification does not teach how to make any "active fragment", "variant", "analog", "derivative" of all TNF alpha and IL-1 beta (claim 10) for the claimed method. One skill in the art know how to isolate and procure the specific TNF, IL-1 beta. There is no recognition in the art that sequence with identity predicts biological function. Attwood et al teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Skolnick et al., teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). Given the unlimited number of undisclosed "variant", "analog" and "derivative" of TNFalpha and IL-1bata is effective for the claimed method. Given the ulimited number of cytokine and retoid combination, it is unpredictable which combination is effective for affecting the physiology of antigen-presentign cell in animal as a method to inhibit or to stimulate the immune system. Further, there is a lack of in vivo working example demonstrating that the claimed method is effective for modulating the immune system may be used to treat "...a physical disorder that may be delayed, prevented, cured or otherwise treatd by differentially modulating immune function. For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention.

In response to applicant's argument on page 11-13 that the examiner admits at page 2 of the Office action that the present specification discloses a method for inhibitng retinol-induced apoptosis of dendritic cells as well as a method for enhancing antigen presentation in dendritic cells, it is noted none of the rejected claims recite a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARa selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid, for example.

In contrast to applicant's assertion that there is no undue experimentation udner Wand, in addition to the lack of guidance with respect to how to make the "analog", "variant", "derivative" of TNF alpha and IL-1, the lack of guidance with respect to how to use the specific combination and "effective amount" of retinoid and cytokine that would either stimulate or inhibit the immune system, and the lack of in vivo working example, the specification does not teach how to extrapolate in vitro data obtained from in vitro induction of apoptosis to the method of modulating the immune response in humans commensurate in scope with the claimed invention. There is insufficient guidance based on in vitro characterization assays to direct a peson of skill in the art to select particular retinoids and cytokine combination as essential for in vivo modulation such as inhibition or stiumulation of immne system to treat any physical disorder.

The written decription rejection of Claims 1-2, 4-5, 10 and 16 stand rejected under 35 U.S.C. 112, first paragraph for the same reasons of record.
Applicant's arguments filed 11/2/04 have been fully considered but are not found persuasive. Applicants' position is that the present specitkation describes the structures of a large number of retinoids, including RAR agonists (selective for (alpha, beta and/or gamma

RARs, or pan RAR agonists), RXR agonists and RAR antagonists. Citations for descriptions and/or methods of synthesizing these agonists and antagonists are also disclosed. Additionally, the specification discloses a number of methods to screen candidate retinoid and cytokine compounds and antigen-presenting cells for their usefulness in the presently claimed methods. Specifically, these methods are used to determine which specific combinations of retinoid and cytokine compounds will have a stimulating or inhibitory effect on antigen-presenting cells. As detailed above, because both nucleotide sequences and three-dimensional protein structures for cytokines are well known in the art, sufficient written description exists in the specification such that fully active variants, analogues and derivatives of cytokines can be produced and used in the method of the invention. Finally, the specification discloses a method for inhibiting retinol-induced apoptosis of Langerhans cells, as well as a method of enhancing antigen presentation in Langerhans cells.

In response, althought the specification discloses a number of retenoids, and cytokines, there is inadequate written description about the structure associated with function of all "agonist", "antagonist", "analog", "derivatives", and "active fragment" of all cytokine without the amino acid sequence or nucleotide sequence. The specification discloses only the specific combination of the specific retinoids and the specific inflammatory cytokine such as TNF alpha and IL-1 wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARa selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid for inhibiting the retinol induced apoptosis. The specification also disclsoes a specific combination of pan RXR agonist SR11237 and an inflammatory cytokine TNF alpha or the specific RARa antagonist BMS749 and an inflammatory cytokine TNF alpha for a method of stimulating antigen presentation. However, there is insufficient written description about the combination of "effective amount" of all retinoid and "effective amount" of all cytokine that affect the physiology of all antigen presenting cell in an animal as a method to modulate such as to inhibit or to stimulate which immune response in all animal. Although the specification discloses various screening methods, the specification does not describe how to make any "analog", "variant", "derivative" of TNF alpha and IL-1 for the claimed method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived.

Claims 1-2, 10 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dunlop et al (Exp Dermatol 3(5):204-11, Oct 1994; PTO 892) in view of Zhou et al (Proc. Natl. Acad. Sci USA 93: 2588-2592, March 1996; PTO 892) or Hausser et al (Immunobiology. 197(5):534-42, Nov 1997; PTO 892) or Cumberbatch et al (Arch Dermatol Res. 289(5):277-84, Apr 1997; PTO 892) for the same reasons of record.

Applicant's arguments filed 11/2/04 have been fully considered but are not found persuasive. Applicants' position is that the cited references provides no suggestion or motivation to one of ordinary skill to combine their disclosures, nor is there knowledge generally available to those of ordinary skill in the art that provides such motivation or suggestion. There is also no express or implicit suggestion of a reasonable likelihood of success in making or using the claimed invention as a result of combining the cited references. One of ordinary skill in the art would not have reconstructed the claimed invention based on the combination of the references cited without using knowledge gleaned from the Applicants' disclosure. This is impermissible hindsight reconstruction that fails to establish aprimafacie case of obviousness.

In response to applicants' arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Duplop pertaining to the method of modulating the immune system of an animal such as mice by affecting the physiology such as cell maturation and allogeneic cell-stimulating capability of antigen-presenting cell such as Langerhans cell from the skin by administering a retinoid such as all-trans retinoic acid and the teachings of Zhou et al indicating success in inducing antigen presenting cell such as monocyte derived dendritic cell differentiation by administering cytokines such as GM-CSF, IL4 or TNFa (See Figure 4B, page 2591, column 1, in particular) or the teachings of Hausser et al indicating success in inducing antigen presenting cell such as monocyte derived dendritic cell (mdDC) activation by administering cytokines such as TNF (See abstract, in particular) or the teachings of Cumberbatch et al indicating success in inducing antigen presenting cell such as Epidermal Langerhans cells (LC) differentiation as measured by acquisition of a more dendritic morphology by treating with TNF-alpha and IL-1 (See abstract, in particular). The success in inducing APC differentiation and activation taught by the cited references would have led one of ordinary skill in the art at the time the invention was made to combine the references to modulate the immune system by affecting the physiology of antigen-presenting cells. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

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